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Effects of Perinatal Methimazole Exposure on a Developmental Test Battery for Neurobehavioral Toxicity in Rats

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Effects of Perinatal Methimazole Exposure on a Developmental Test Battery for Neurobehavioral Toxicity in Rats. COMER, C. P., AND NORTON, S. (1982). *Toxicol. Appl. Pharmacol.* 63, 133–141. The antithyroid drug, methimazole, was investigated to assess its potential as a positive control agent in developmental behavioral studies. Methimazole was administered in drinking water to dams from the 17th gestational day to the 10th postnatal day. Methimazole treatment produced developmental delays and motor deficits in offspring tested in a behavioral battery assessing development of sensory and motor function. Acquisition of a righting response was delayed 7 days, from postnatal Day 7 in controls to Day 14 in treated rats; the appearance of the auditory startle response was delayed 6 days, from Day 12 to Day 18; the time of eye opening was delayed 2 days, from Day 15 to Day 17. A deficit, rather than a delay, was observed in body weight gain and in a reflex-suspension test of motor development. Treated rats showed decreased exploratory activity in an open field at postnatal Day 21 compared with controls. It was concluded that developmental test batteries, such as those proposed to screen for neurobehavioral toxicity, may readily detect neurotoxic damage from goitrogens. The convenience of methimazole administration in drinking water plus the efficacy of methimazole inducing developmental deficits and delays suggests this agent may be an effective positive control in developmental behavioral test batteries.

Developmental test batteries have been suggested for assessment of the functional status of the developing nervous system after perinatal insult (Spyker, 1975; Culver and Norton, 1976; Buelke-Sam and Kimmel, 1979; Vorhees *et al.*, 1979; Grant *et al.*, 1980). A basic assumption of these developmental test batteries is that the failure of a function to develop, or the delayed appearance of a function after exposure to a toxicant, reflects uncompensated damage to the developing nervous system. The distinction between failure to develop and delayed appearance often may not be made.

Rodents exposed perinatally to antithyroid agents demonstrate marked developmental delays (Eayrs and Lishman, 1955; Essman *et al.*, 1968). In contrast, the results of neurological test batteries done on rats exposed to agents which produce neurological damage, such as after carbon monoxide (Culver and Norton, 1976) or hydroxyurea (Vorhees *et al.*, 1979), demonstrate equivocal functional deficits or show no evidence of developmental delay.

Perinatal administration of goitrogens to pregnant and lactating dams produces a reversible thyroidectomy in neonates. This condition allows thyroid hormone levels to be reduced during the critical perinatal pe-

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riod when thyroid hormones are necessary for normal brain development (Eayrs, 1966; Essman *et al.*, 1968). Methimazole is a clinically used antithyroid agent which can induce hypothyroidism in neonatal animals. It is stable and freely soluble in water, and can be administered by daily injection (Hajos *et al.*, 1973; Rastogi *et al.*, 1976), or in drinking water (Grosvenor, 1962; Liv, 1975; Van Middlesworth and Norris, 1980). An advantage of methimazole administered in drinking water is the ease of measuring the volume consumed versus measuring food consumption which involves considerable spillage and waste. In addition, the potential of trauma to neonates by daily injection is also avoided.

The placental transfer of methimazole is more efficient than that of other antithyroid agents, such as propylthiouracil. Marchant and co-workers (1977) found the fetal serum/maternal serum ratio of methimazole approached 1.0, 20 min after an iv injection into pregnant rats on the 19th day of gestation. In the same series of experiments, the fetal serum/maternal serum ratio of propylthiouracil reached a maximum of 0.7 at 60 min after injection.

In this study, methimazole was administered in drinking water to pregnant and lactating dams. The hypothesis was that a chemical expected to delay CNS maturation would be detected readily by a neurological developmental test battery similar to those proposed for detection of various toxic insults to the CNS. Should this hypothesis be valid, hypothyroidism from methimazole administration during early development would provide a positive experimental control for developmental test batteries proposed as general screens for developmental neurotoxicity.

METHODS

Breeding and Methimazole Administration

Female, Sprague–Dawley-derived rats weighing about 150 g were purchased from Charles River Breeding Laboratories. The rats were allowed to acclimate to animal housing quarters until body weights of about 200 g were reached. Two females were placed into breading cages containing one established resident male. Rats were paired late in the afternoon and were not disturbed until the following morning. Estrous cycle was then determined daily between 8 and 9 AM by vaginal lavage until a female was observed to be sperm positive. Females observed to be sperm positive were assigned "gestational day 1," removed from breeding cages, and housed singly in plastic laboratory cages for the duration of gestation.

Sixteen pregnant rats were randomly assigned to either control or experimental groups. Starting on gestational Day 15, tap water was replaced with distilled water and the volume consumed was recorded daily. On gestational Day 17, eight animals (controls) continued to receive distilled water and eight animals (treated) were begun on a 0.1 mg/ml solution of methimazole.[3] This concentration was calculated to provide a daily methimazole dose close to concentrations reported to inhibit the thyroid (Grosvenor, 1962; Liv, 1975; Van Middlesworth and Norris, 1980). Methimazole administration in drinking water was continued throughout the perinatal period from the 17th gestational day to the 10th postnatal day. Liquid consumption was recorded for both control and treated animals. The fluid consumption prior to parturition ranged from 46 to 88 ml/rat/day for methimazole treated and 52 to 110 ml/rat/day for control rats. The range in the first 4 postnatal days was 35 to 80 ml/rat/day for methimazole-treated and 40 to 90 ml/rat/day for control rats. In postnatal Days 5 to 10 the range for methimazole-treated rats was 62 to 100 ml/rat/day and 60 to 130 ml/rat/day for control rats. The eight control rats averaged 0 to 15% more daily fluid consumption before parturition than the eight methimazole-treated rats. After parturition the daily average of the control rats was 15 to 20% more liquid. Since fluid consumption varied widely from day to day in both groups, the differences were not significant on a daily basis. However, the overall lower fluid consumption after parturition of the rat drinking methimazole may have been due either to a taste aversion or to a lower demand during lactation because of the smaller size of the methimazole-treated pups. Because the differences in fluid consumption were small and were comparable in magnitude to the smaller size of the treated pups, no paired adjustment for fluid intake was made between the two groups of rats.

Prior to parturition, pregnant females were provided with paper strips for nest building material. The duration of gestation, number of live pups, and observed dead fetuses were recorded.

[3] Methimazole was kindly provided by Dr. Gerard Poore, Eli Lilly Research Laboratories, Indianapolis, Ind.

TABLE 1

NEUROLOGICAL DEVELOPMENTAL BATTERY

Parameter measured	Postnatal period of testing
Body weight	Daily (postnatal Days 1–24) Weekly (4, 5, 6 weeks)
Righting response	Daily (Day 1 to criterion)
Reflex suspension	Daily (postnatal Days 7–14)
Auditory startle	Daily (Day 10 to appearance)
Eye opening	Day both eyelids separated
Open field activity	Day 21

Developmental Observations

Eighteen to 24 hours after birth, litters were culled to eight pups, four males and four females or three and five of either sex in the two instances where the number of males or females was insufficient. At this time, testing with a neurological developmental battery was begun (Table 1). This battery is similar to others described to measure neurological and reflex development in rats and is based on studies of normal rat development (Eayrs and Lishman, 1955; Fox, 1965). Blind testing was not employed, in keeping with the all-or-none nature or objective measurements in the tests.

Surface righting response was determined by placing the rat on its back on a smooth surface. The time required for the rat to right itself with all four feet flat on the surface was determined. Each pup was allowed three trials and the time of the best effort was recorded. The surface righting response was measured daily from 24 hr after birth until a criterion of 0.5 sec righting time was reached by both control and treated animals. A maximum of 60 sec per trial was allowed.

Reflex suspension was determined daily between postnatal Days 7 and 14 as a measure of motor development, grip, and quadripedal strength prior to eye opening. The front feet of the animal were touched to a 2-mm metal rod suspended above a cushion of bedding, and the rat was allowed to grasp the rod. Each animal was given three suspension trials with a maximum of 60 sec of suspension per trial. The time of the longest suspension was recorded.

Auditory startle was tested once daily from postnatal Day 10 until its appearance. The test was repeated when the result was ambiguous. The rat was placed in a glass beaker and a loud, sharp noise was produced by a metal rod being tripped to fall a distance of 3 cm onto an aluminum plate suspended above the beaker. The animals were tested for a response to the noise in the form of a jump or startle only when standing on all four feet, since the auditory startle response is largely mediated through the upper body and may not be observed while the animal is rearing.

Eye opening was recorded as the day both eyelids were observed to be well separated.

Open field observations were made as a measure of spontaneous exploratory activity. Twenty-one-day-old animals were placed in the center four squares of a 60 by 60-cm open field marked off into 5-cm squares. The total number of squares entered with both front feet during a 10-min observation period was recorded. This test was initiated part way through the postnatal studies; five control and six treated litters were studied.

Statistics

Statistical comparisons were made using Student's *t* test for comparison of means and by a two-way analysis of variance with repeated observations (BMD Statistical Package) for other observations.

RESULTS

Perinatal Observations

The eight control and eight treated females consumed similar amounts of fluid before and during methimazole administration periods. The average daily consumption of methimazole in drinking water was calculated from the volume of fluid consumed by treated females (Fig. 1). The values re-

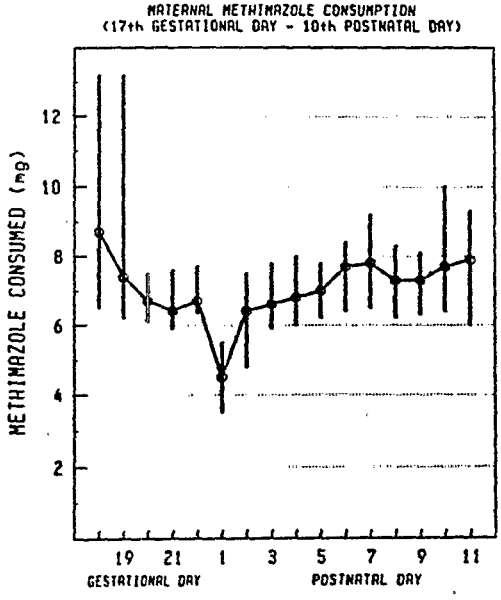

FIG. 1. Daily methimazole consumption by pregnant females from gestational Day 17 to postnatal Day 10. Points are means (± range) for eight treated females.

TABLE 2

REPRODUCTIVE DATA

	Control	Methimazole	
Number of litters	8	8	—
Duration of gestation	22.6 ± 0.3[b]	22.1 ± 0.1	NS
Range (days)	22–24	22–23	
Live pups (at 24 hr)	13.6 ± 0.9	13.1 ± 0.6	NS
Range	9–17	10–15	
Live pups (at 11 days)[a]	7.4 ± 0.2	7.5 ± 0.2	NS
Range	7–8	7–8	

[a] Day after methimazole administration was discontinued.
[b] $\bar{x}$ (±SE).

corded for each day reflect the volume consumed during the previous 24-hr period. Perinatal methimazole treatment had no apparent effect on the duration of gestation, the number of live pups delivered, and pup viability (Table 2). Both control and treated pups were observed to suckle and had visible milk in their stomachs by 24 hr after birth.

Developmental Observations

Body weights. There was a significant reduction in body weight for male and female pups from the fourth postnatal day until maturity (Fig. 2). Both male and female treated pups showed approximately a 20% reduction in body weight and this decrease was constant throughout the developmental period.

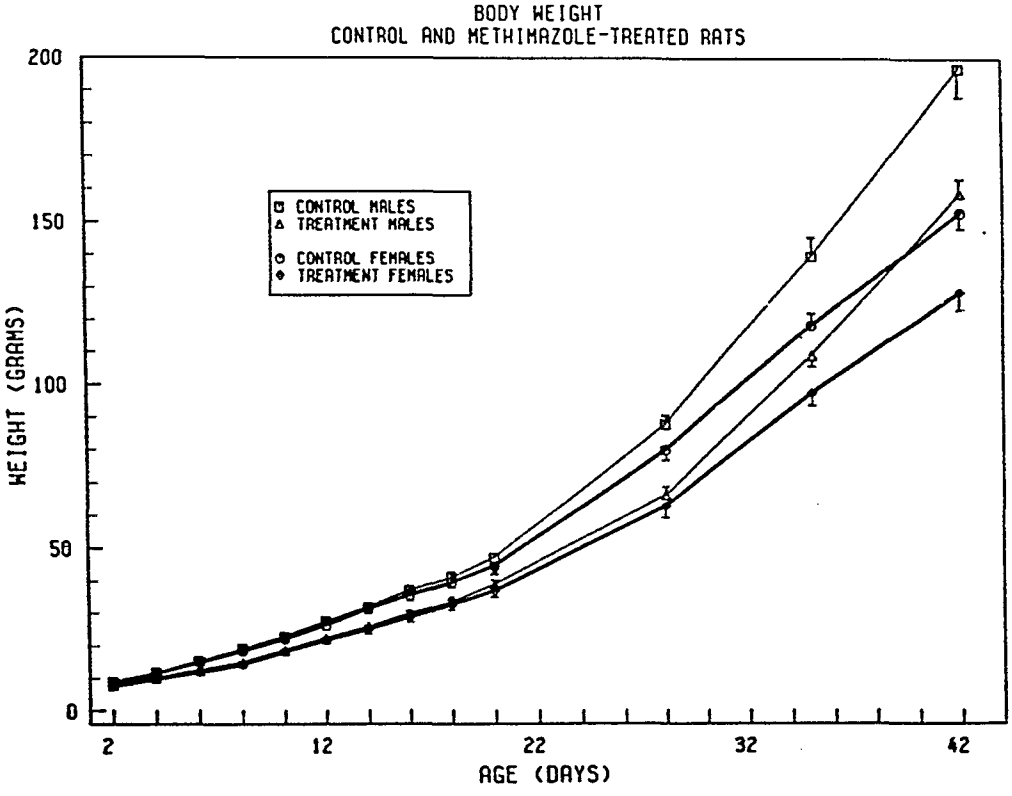

FIG. 2. Growth of control rats and treated rats from litters where the only drinking solution available to dams from gestational Day 17 to postnatal Day 10 was either distilled water or a 0.1 mg/ml solution of methimazole. Heavy lines are weights of female rats, lighter lines are weights of male rats. Points are litter means (±SE) for eight litters (six to eight animals per litter). Body weights of both male and female methimazole-treated rats were significantly reduced ($p < 0.05$) at every point after postnatal Day 2.

Surface righting response. Control rats showed a progressive improvement in righting response performance from 24 hr after birth (Fig. 3). Treated rats had a poorer righting response time on the second day than on the first. Righting response times were significantly longer for treated animals from the 2nd to the 13th postnatal day. By the 5th postnatal day, treated rats had a performance equivalent to 24-hr controls. Treated rats reached the 0.5 sec average righting response criterion at Day 14 while control rats reached this criterion by Day 7. No difference was observed between sexes for either control or treated pups.

Reflex suspension. The mean daily suspension time was significantly lower for treated rats at every test interval between Days 7 and 14 (Fig. 4). Control rats showed a progressive improvement in suspension time during the one-week testing period; treated rats showed only slight improvement. No sex-related differences were observed for either control or treated groups.

Auditory startle response. Acquisition of the auditory startle response was delayed an average of 6 days in treated rats compared with controls. Control animals showed a startle response by Day 12 whereas the average time of appearance in treated animals was Day 18 (Table 3). Some early responding control animals showed a startle on Day 10 and some late responding treated animals did not acquire the startle response until Day 21. All pups, both control and treated, developed a startle response at some point during the developmental period. No sex-related differences were observed for the startle response acquisition.

Eye opening. The first day when eylids were well separated was significantly delayed in treated pups. In Table 4, the mean delay was almost 2 full days for male and female treated pups compared with controls. There were no sex-related differences in the time of eye opening in control or treated groups.

Open field. Treated males and females were significantly less active than controls of the same sex during a 10-min period of observation in an open field (Table 5). Control males were less active than control females and treated males were less active than treated females. This finding might rep-

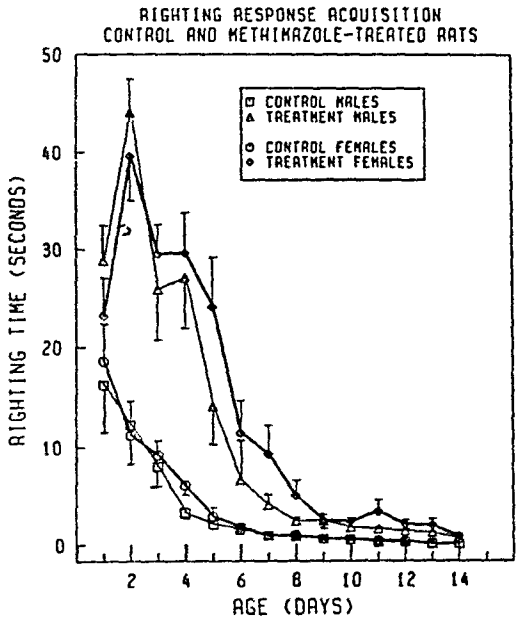

FIG. 3. Surface righting response acquisition for control rats and treated rats exposed to methimazole perinatally. Heavy lines are righting times for female rats, lighter lines are righting times for male animals. Points are litter means (±SE) for eight control or eight treated litters (six to eight animals per litter). Righting times were significantly increased ($p < 0.05$) for methimazole-treated pups on Days 2–13.

TABLE 3

AUDITORY STARTLE RESPONSE ACQUISITION

	(Day ± SE)		
	Control	Methimazole	
Female	11.8 ± 0.2	18.1 ± 0.5	$p < 0.001$
Male	12.1 ± 0.2	18.1 ± 0.6	$p < 0.001$

Note. N = eight control, eight methimazole-treated litters.

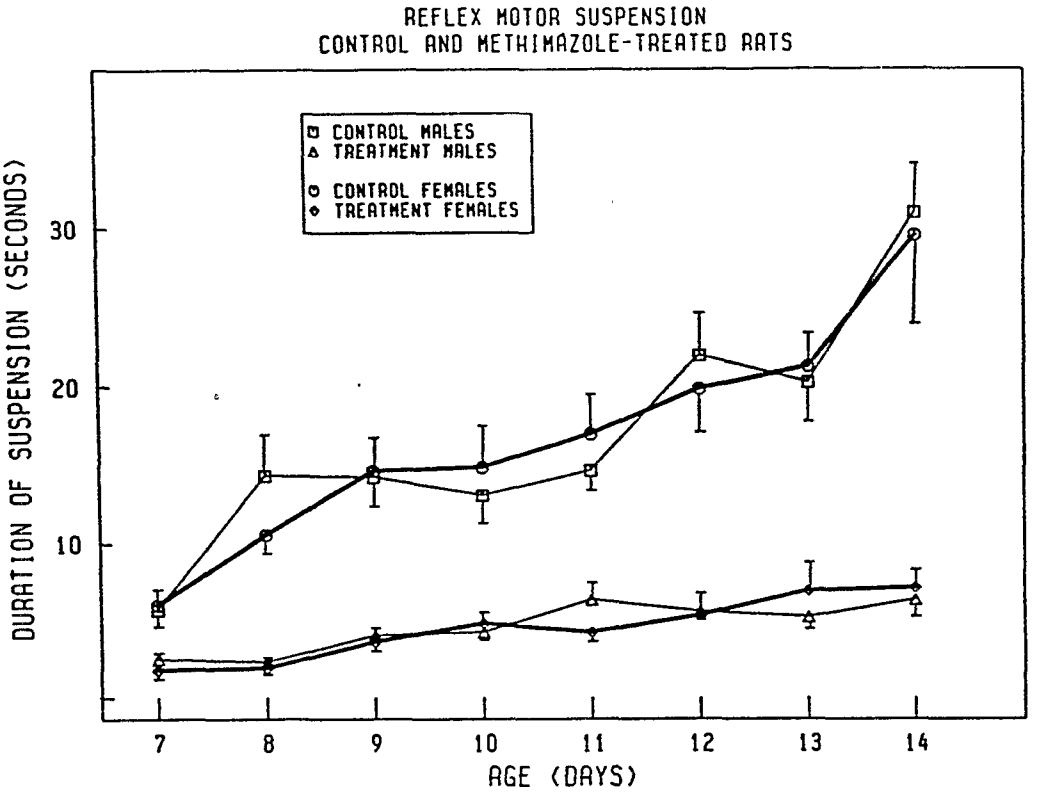

FIG. 4. Reflex suspension times for control rats and treated rats exposed to methimazole perinatally. Heavy lines represent times for female rats, lighter lines are times for male rats. Points are litter means (±SE) for eight control and eight treated litters (six to eight animals per litter). Methimazole-treated pups had significantly decreased ($p < 0.05$) suspension times on every test day.

resent, in these sexually immature animals, the beginning of a typically adult pattern of open field exploratory activity where males are normally less active than females. Control animals tended to explore more of the open field area than did treated rats. Both male and female treated rats spent a great deal of time sitting still in the corners of the open field. When a treated rat did show activity, it was very often a rapid movement along an exterior wall directly to the next corner where the animal again stopped. Control animals engaged in more continuous movement over a greater portion of the open field than did treated rats.

TABLE 4

EYE OPENING

	(Day ± SE)		
	Control	Methimazole	
Female	15.0 ± 0.2	16.9 ± 0.2	$p < 0.001$
Male	15.1 ± 0.2	16.7 ± 0.2	$p < 0.001$

Note. N = eight control, eight methimazole-treated litters.

DISCUSSION

Perinatal administration of methimazole to female rats produced marked alterations in the onset of developmental milestones in their offspring. The retardation of the ap-

pearance of the righting response, the delayed acquisition of the startle response, and the delayed time of eye opening can all be classified as developmental delays since methimazole-treated animals achieved the same performance as control animals but at a later time. The performance in the test of motor development (reflex suspension) and the decreased body weight gain in methimazole-treated pups suggest functional deficits rather than delays. Early hypothyroidism involves not only developmental delay, but permanent functional deficits as well. The clinical picture of permanent mental retardation after untreated cretinism is well known (Fisher, 1978).

Male and female treated rats showed decreased activity in an open field at 21 days of age when compared with same-sex controls. Rastogi and colleagues (1976) measured activity in an open field at 7, 15, and 30 days of age following early methimazole treatment. Control animals showed a sixfold increase in open field exploratory activity between 7 and 30 days of age. The activity of methimazole-treated rats was equivalent to euthyroid controls on Day 7 but increased less than twofold by Day 30. As a result, treated animals were hypoactive compared with controls on Days 15 and 30. Comparable results are reported for 21-day-old, methimazole-treated rats in the current study.

Eayrs and Lishman, in an early study (1955), definitively demonstrated the developmental delay in hypothyroid animals. These authors used three experimental groups of rats: euthyroid controls, rats made hypothyroid by either methylthiouracil or iodine-131 injection, and "starved" rats which served as weight-matched controls with hypothyroid animals. The pattern observed by Eayrs and Lishman in this early developmental battery of tests was a consistent delay in attainment of criterion performance in developmental tasks after antithyroid treatment. Starved rats showed a developmental delay as well but to a lesser degree than did hypothyroid animals. The overall performance of starved rats more closely approximated that of control animals.

TABLE 5

OPEN FIELD ACTIVITY

	Squares entered during a 10-min observation period (±SE)		
	Control	Methimazole	
Female	635 ± 83	381 ± 26	$p < 0.01$
Male	436 ± 57	186 ± 38	$p < 0.01$

Note. 21-day-old control and methimazole-treated rats. N = five control, six methimazole-treated litters with results from two or three male and female rats averaged per litter.

Studies in addition to that of Eayrs and Lishman (1955) have confirmed that severe undernutrition alone can produce mild developmental delay. "Starved" or "weight-matched" controls have been used to compensate for the weight difference observed between euthyroid controls and hypothyroid animals (Levitsky *et al.*, 1975; Rosman and Malone, 1977; Legrand *et al.*, 1980). Behavioral results obtained from reduced weight groups, however, consistently approximate euthyroid control animals.

As noted in the Introduction, developmental testing batteries, such as used in this study, have been most successful in detecting damage which results in maturational delays. Developmental delay in weight gain and the time of vaginal opening has been observed after prenatal exposure to polybrominated biphenyls (PBBs) in rats (Harris *et al.*, 1978). A dose-related retardation in weight gain, motor development, and time of eye opening was observed in mice after perinatal exposure to lead (Maker *et al.*, 1975). Maturational delays have been observed following perinatal ethanol exposure, as associated with the fetal ethanol syndrome, both clinically (Clarren and Smith, 1978) and in rats (Lee *et al.*, 1980). Devel-

opmental delay has also been observed after extreme malnutrition during pregnancy (Eayrs and Lishman, 1955; Levitsky *et al.*, 1975), after maternal restraint-induced stress during pregnancy (Barlow *et al.*, 1978), and after postnatal injections of cortisol acetate (Salas and Schapiro, 1970). All of the above cited conditions associated with developmental delay, with the exceptions of maternal stress and postnatal cortisol injections, are known to decrease thyroid function (Shambaugh and Wilber, 1974; Goldman *et al.*, 1977; Wastell *et al.*, 1978; Kornguth *et al.*, 1979).

There is a virtual absence of reports in the literature where agents which act by known mechanisms other than causing physiological (hormonal) alterations in the fetal CNS, produce deficits readily detectable by neurological developmental batteries. When results of developmental testing batteries have been published for agents which produce fetal neuronal death or fetal neuronal genetic damage, the results have been either negative or equivocal, for example in reports of postnatal testing after carbon monoxide (Culver and Norton, 1976), monosodium glutamate, calcium carragenan, and hydroxyurea (Vorhees *et al.*, 1979). Even animals which have grossly visible ectopias of the cerebral cortex, as after prenatal X irradiation (Schneider and Norton, 1979) or of the caudate nucleus, as after prenatal carbon monoxide (Daughtrey and Norton, 1981), show little or no functional damage detectable by the neurological developmental testing battery used in the present experiments. This finding does not demonstrate that these animals do not have neurological or functional deficits; it simply points out the selectivity of developmental testing batteries for deficits produced by agents which cause developmental delay.

In conclusion, perinatal methimazole administration produces developmental deficits and delays which are easily detectable by tests normally included in developmental behavioral batteries. This observation suggests that agents which produce perinatal hypothyroidism may be effective positive controls for functional toxicity of potentially neurotoxic substances.

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